

Please add new claim 36.

Q2 36. A compound according to claim 1 wherein R is methyl or ethyl; R<sub>1</sub> is fluoro; R<sub>2</sub>-R<sub>4</sub> are hydrogen or fluoro; and R<sub>5</sub> is chloro or fluoro; or a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable prodrug ester thereof.

REMARKS

Reconsideration of the application as amended is respectfully requested.

The claims under consideration are claims 1-35. The allowability of claims 20-35 is gratefully acknowledged.

Claim 20 has been made independent and a clerical error has been corrected with respect to the designation assigned to the structural formula so as to conform to the designation on page 5 of the specification.

As far as the subject matter of claims 1-19, claims have been amended to more particularly claim the invention.

Claim 1, and claims dependent therefrom, have been amended with respect to R<sub>3</sub> and R<sub>5</sub>, from the definitions of which hydroxy and methyl, respectively, have been deleted.

Claim 9, which is no longer encompassed by amended claim 1, has been cancelled without prejudice of Applicants' rights relating thereto; the same applies to dependent claim 14.

Claim 31 has been amended for consistency with the other claims.

Claim 36 (dependent from claim 1) has been added to claim a particular aspect of the invention. Support appears on page 4 of the specification (third paragraph from bottom of page).

Reconsideration of the rejection of claims 1-19 under 35 USC 103(a) as being unpatentable over EP 865,788 (Yamazaki), DE 3,445,011 (Ciba-Geigy AG), and US 3,558,690 (Sallmann et al.) is respectfully requested.

Said claims pertain to 5-(methyl or ethyl)-2-(substituted anilino)-phenylacetic acids (formula I) as cyclooxygenase 2 (COX-2) selective cyclooxygenase inhibitors.

Yamazaki discloses 2-(2,6-dichloro-4-hydroxyanilino)-phenyl-acetic acid to be a "specific" cyclooxygenase-2 (COX-2) inhibitor in comparison to 2-(2,6-dichloroanilino)phenylacetic acid (diclofenac), a potent inhibitor of both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). While the introduction of the 4-hydroxy group into the diclofenac molecule apparently results in COX-2 selective cyclooxygenase inhibition, such structural modification leads to a considerable decrease in potency of such inhibition (Tables 1 and 2). It is therefore respectfully submitted that Yamazaki would not suggest the desirability of preparing other 4-hydroxyanilino-substituted compounds, in particular not 4-hydroxyanilino-5-(methyl or ethyl)-substituted compounds of the instant invention.

However, in order to facilitate and expedite the prosecution, compounds of formula I wherein  $R_3$  (the 4 substituent) is hydroxy have been cancelled from the instant claims.

It is therefore respectfully submitted that Yamazaki would not render obvious any subject matter of the instant amended claims, either alone or in combination with the other applied citations.

Sallmann et al. (US 3,558,690) discloses a series of 2-(substituted anilino)-phenylacetic acids optionally substituted on the phenylacetic acid ring by " $R_4$ ", namely (lower) alkyl, (lower) alkoxy, chloro, fluoro or bromo, at any of the available ring positions.

It is recognized that a partial overlap exists between certain compounds of the instant claims and the broad generic disclosure of Sallmann et al. with respect to the compounds of formula IA therein wherein " $R_4$ " represents (lower) alkyl. No overlap exists with respect to compounds of formula IB therein.

As to specific compounds disclosed by Sallmann et al. wherein " $R_4$ " represents (lower) alkyl, only 5-methyl-2-(2,6-dimethylanilino)-phenylacetic acid and salt thereof (examples 11f and 12) is seen therein.

In addition, no preference is indicated for any compounds wherein " $R_4$ " is (lower)-alkyl. As a matter of fact, such are not encompassed by the subgeneric claims 4-19 of Sallmann et al. which are limited to compounds wherein " $R_4$ " is hydrogen or chloro.

In this connection, the Applicants would like to call to the Examiner's attention, Moser et al., J. Med. Chem. 33, 2388 (1990) submitted by the Applicants with Information Disclosure Statement dated November 23, 1998 and which should be considered in conjunction with Sallmann et al. Biological data is presented for compounds encompassed by US 3,558,690 (Sallmann et al.). While data is presented e.g. for 2-(2,6-dimethylanilino)phenylacetic acid (compound No. 12, Tables I and II), none is given for the corresponding 5-methyl-2-(2,6-dimethylamilino)phenylacetic acid of Sallmann et al. The lack of any data provides no guidance and would certainly not suggest the desirability of preparing any other 5-alkyl substituted compounds. Moser et al. would in fact serve to discourage one of ordinary skill from choosing to prepare any of the 5-(methyl or ethyl)-substituted compounds of the instant claims.

In order to facilitate and expedite prosecution of the instant application, the rejected claims have been amended to exclude compounds wherein R<sub>5</sub> (the substituent of the 6-position) in formula I represents methyl. Neither the 2 nor the 6 substituent of the anilino phenyl ring now represents methyl in the instant claims, whereas both are methyl in the only 5-methyl substituted species disclosed by Sallmann et al.

In view of all the above, it is respectfully submitted that Sallmann et al. would not render obvious any of the subject matter of instant amended claims 1-8, 10-13, 15-19 and 36.

DE 3,445,011 is specifically directed to 2-(2-chloro-6-fluoroanilino)-phenylacetic acid which is described to demonstrate a more favorable ulcer index for gastrointestinal tolerance than diclofenac, which is 2-(2,6-dichloroanilino)-phenylacetic acid of Sallmann et al.

It is respectfully submitted that DE 3,445,011 alone would not suggest a 5-(methyl or ethyl)-substituted derivative thereof.

As to DE 3,445,011 in combination with Sallmann et al., Sallmann et al. (especially when considered in conjunction with Moser et al. as discussed above) would not teach or suggest the desirability of — and does not provide the necessary motivation to one of ordinary skill in the art for — the structural modification to a corresponding 5-(methyl or ethyl)- substituted -2-(2-chloro-6-fluoroanilino)phenylacetic acid.

It is therefore respectfully submitted that DE 3,445,011 either alone or in combination would not render obvious any of the subject matter of the instant claims.

In view of all of the above, it is respectfully submitted that the above-cited references — either alone or in combination — would not suggest to one of ordinary skill in the art — without inadmissible hindsight reliance on the Applicants disclosure — the desirability of preparing, and would not render obvious any of the compounds of the instant amended claims.

It is further respectfully submitted that the applied references would not render obvious any of the pharmaceutical composition, method of use and process claims relating thereto (claims 10-13 and 15-19). In this connection, it should be noted that aside from Yamazaki, none of the citations relate to selective COX-2 inhibition.

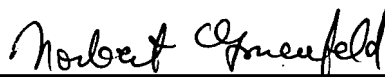
It is therefore respectfully submitted that the rejection applied to claims 1-19 (instant claims 1-8, 10-13, 14-19 and 36) under 35 USC 103(a) is no longer warranted and should be withdrawn.

It has been noted that the claim for domestic priority under 35 USC 119(e) has not been acknowledged in the Office Action. The claim is set forth in Applicants' Declaration and on page 1 of the specification.

Also, the Applicants would appreciate receiving a confirmation of the Examiner's consideration of all the citations listed on 1449 forms which were submitted to the PTO with Information Disclosure Statements dated November 23, 1998, December 3, 1998 and March 2, 1999.

It is now believed that all the instant claims are in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,



Norbert Gruenfeld  
Agent for Applicants  
Reg. No. 30,061

Novartis Corporation  
Patent and Trademark Dept.  
564 Morris Avenue  
Summit, NJ 07901-1027  
(908) 522-6926

NG:mjl

Date: December 7, 1999

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